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Ulipristal Acetate
In Uterine Fibroids

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Contents

Abstract

Ulipristal acetate, a selective progesterone-receptor modulator, inhibits the proliferation and induces apoptosis of leiomyoma cells *in vitro*. It also modulates the expression of vascular endothelial growth factors and hormone receptors and modulates extracellular matrix breakdown in leiomyoma cells but not in myometrial cells.

In two randomized, double-blind, multinational phase III trials of 13 weeks' duration in women aged 18–50 years with uterine fibroids, a once-daily regimen of oral ulipristal acetate 5 mg/day controlled excessive uterine bleeding (primary endpoint) in ≥90% of patients. Ulipristal acetate 5 mg/day was more effective than placebo and was shown to be noninferior to intramuscular leuprolide acetate 3.75 mg once monthly in controlling uterine bleeding.

Uterine bleeding was rapidly controlled by ulipristal acetate. Approximately half of recipients of ulipristal acetate 5 mg/day became amenorrhoeic within the first 10 days of treatment. Furthermore, uterine bleeding was controlled significantly more rapidly for recipients of ulipristal acetate than recipients of leuprolide acetate.

A significantly greater median reduction from baseline in total fibroid volume was observed for recipients of ulipristal acetate 5 mg once daily than recipients of placebo following 13 weeks' treatment (coprimary endpoint). For patients who did not undergo surgery, the volume reduction was maintained for at least 6 months after discontinuing treatment.

Ulipristal acetate was generally well tolerated in women with uterine fibroids. The incidence of hot flush occurred with a significantly lower frequency for recipients of ulipristal acetate than for recipients of leuprolide acetate.

Features and properties of ulipristal acetate (Esmya™)	
Featured indication	
Pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age	
Mechanism of action	
Selective progesterone-receptor modulator	
Dosage and administration	
Route of administration	Oral
Dose	5 mg
Frequency of administration	Once daily for up to 3 months
Pharmacokinetic profile (oral administration of a single 5 mg dose) in the fasted state. All values are means, unless stated otherwise	
Peak plasma concentration (C_{max})	23.5 ng/mL
Median time to C_{max}	≈1 h
Area under the plasma concentration-time curve from time zero to infinity	61.3 ng • h/mL
Clearance	≈100 L/h
Terminal elimination half-life	≈38 h
Most frequent adverse events	
Amenorrhoea, endometrial thickening, headache	

Uterine fibroids (leiomyomas) are the most common form of benign gynaecological tumours and occur in 20–40% of women of reproductive age. They are mostly derived from myometrial smooth muscle cells and connective tissue fibroblasts and characteristically present as well encapsulated fibrotic tissue within the wall of the uterus.[1] Although there is some evidence that they may arise by somatic mutation,[2,3] fibroids are associated with a low propensity for malignant transformation.[4,5] African-American women have a higher risk of developing fibroids than Caucasian women, which indicates there may be a genetic link.[6,7]

Many uterine fibroids go undiagnosed, and the majority of women are asymptomatic.[8] However, approximately 20–50% of women with fibroids will require some kind of clinical intervention.[8] In these women, the most common symptoms are menorrhagia and iron-deficiency anaemia, which may lead to chronic fatigue.[9] Other symptoms, such as pelvic pain and dysmenorrhoea and pressure effects, which may lead to urinary problems, also have a significant impact on quality of life.[10,11] In addition, women with fibroids may experience a higher risk of infertility, miscarriage, preterm deliveries and complications in late pregnancy.[10,11]

Symptomatic fibroids are the leading reason for hysterectomy, accounting for more than one-third of all procedures performed, thus incurring considerable healthcare costs.[12,13] Hysterectomy is the only procedure for permanent removal of fibroids but is not appropriate for women who wish to retain fertility.[14] The surgical removal of fibroids without hysterectomy (myomectomy) is an alternative option for women who wish to become pregnant, but this procedure does not prevent recurrence of the condition.[14] Uterine artery embolization is a less invasive alternative but may compromise pregnancy due to the risk of premature ovarian failure.[15] All of these procedures are associated with considerable postoperative morbidity.[16]

There are several non-surgical treatments for fibroids, both hormonal (contraceptives [either oral or intrauterine devices], progestogens, danazol, aromatase inhibitors, gonadotropin-releasing hormone [GnRH] analogues or mifepristone) or non-hormonal (NSAIDs or antifibrinolytics).[16] However, many of these treatments have questionable efficacy and are associated with adverse tolerability; consequently, the GnRH agonist leuprolide acetate was, until recently, the only approved pharmacological treatment for the condition.[17,18] Therefore, there still remains an unmet need for an effective treatment of fibroids that is both well tolerated in the longer term and that offers women the option of uterine preservation and the retention of fertility.

Although the underlying aetiology is poorly understood, hormonal exposure, over expression of growth factors, or genetic changes may play a role in the pathogenesis of fibroid formation.[19] Fibroids usually develop during the reproductive years and regress following the menopause, implicating a growth-promoting role for estrogen. *In vivo* models have shown that growth hormone may also act synergistically with estrogens in fibroid growth, and the incidence of fibroids is higher in women with acromegaly.[20,21] More recently, several lines of biochemical and clinical evidence have implicated a critical role for progesterone in the pathogenesis of uterine fibroids.[22–27]

Selective progesterone modulators (SPRMs) are a new class of progesterone-receptor ligands that exert tissue-selective agonist, antagonist or mixed agonist/antagonist activity in target cells.[28] This class of compounds has numerous applications in female medicine, including emergency contraception, long-term contraception, termination of pregnancy, premenstrual syndrome and in assisted reproduction.[29,30] Many SPRMs have also been shown to inhibit endometrial cell proliferation and reduce endometriotic lesions in animal studies.[31,32] This property has led to their evaluation for the treatment of uterine fibroids, dysfunctional uterine bleeding and endometriosis.[33]

Ulipristal acetate (Esmya™) is an SPRM that was initially approved as an emergency contraceptive (reviewed by McKeage and Croxtall).[34] It has recently received approval for the treatment of uterine fibroids[35] based on the efficacy outcomes of two pivotal phase III trials, PEARL I (PGL4001 [ulipristal acetate] Efficacy Assessment in Reduction of symptoms due to uterine Leiomyoma)[36] and PEARL II,[37] discussed in section 3. This article provides an overview of the

pharmacological properties of ulipristal acetate and reviews its clinical efficacy and tolerability in women with uterine fibroids.

Medical literature on the use of ulipristal acetate in uterine fibroids was identified by searching databases since 1996 (including MEDLINE and EMBASE), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug. Searches were last updated 17 April 2012.

1. Pharmacodynamic Profile

The pharmacodynamic properties of ulipristal acetate as a contraceptive agent are well documented.[34] Therefore, this section provides an overview of features that are relevant to the management of uterine fibroids. Some data are provided from the Electronic Medicines Compendium (EMC) summary of product characteristics.[35] Randomized placebo-controlled trials in healthy women evaluated the effect of ulipristal acetate 2.5, 5 or 10 mg/day on hypothalamic-pituitary-ovarian axis function following 3 months' treatment (n = 46)[38] and endometrial vascularization following 12 weeks' treatment (n = 41),[39] which are discussed briefly.

- Ulipristal acetate is an orally active SPRM that binds with high affinity to the progesterone receptor where it has both antagonist and partial agonist activity.[34] It has minimal affinity for the androgen receptor and no affinity for the human estrogen or mineralocorticoid receptors.[34] Although in animal models ulipristal acetate has some affinity for the glucocorticoid receptor, no antiglucocorticoid effects have been observed in humans.[34] Furthermore, the glucocorticoid receptor antagonist activity of ulipristal acetate is much lower than that of mifepristone,[40] indicating that it belongs to a new class of progesterone-receptor modulators with dissociated antiglucocortcoid activity.
- *In vitro*, ulipristal acetate inhibits the proliferation of cultured leiomyoma cells by down-regulating proliferating cell nuclear antigen expression and induces apoptosis by increasing cleaved caspase-3 expression and decreasing Bcl-2 expression.[41]
- Ulipristal acetate down-regulates the expression of vascular endothelial growth factors (VEGFs), adrenomedullin and their receptors and modulates the ratio of progesterone isoforms in leiomyoma cells but not in normal myometrial cells.[42] Similarly, ulipristal acetate enhances the breakdown of the extracellular matrix of leiomyoma cells by increasing the expression of metalloproteinases and decreasing the expression of inhibitors of metalloproteinases and collagen, with no comparable effects observed in cultured myometrial cells.[43]
- The principal effect of ulipristal acetate is to inhibit or delay ovulation and induce amenorrhoea without down-regulating estradiol levels or inducing endometrial hyperplasia.[38] The mechanism by which this occurs is not fully clarified, but it may act by inhibiting or delaying the luteinising hormone (LH) surge, postponing LH peak if LH surge has already started, or by directly inhibiting follicular rupture.[44,45]
- Ulipristal acetate inhibited ovulation and normal uterine bleeding in healthy women.[38] Anovulation rates were significantly ($p < 0.001$) higher in the ulipristal acetate 5 and 10 mg/day treatment groups compared with placebo (82% and 80% vs 0%), but not in the 2.5 mg/day treatment group (9%).[38] The mean duration of bleeding in month 3 of the trial was 6.4 days for recipients of placebo compared with 4.2, 1.25 and 0.3 days for recipients of ulipristal acetate 2.5, 5 and 10 mg/day, respectively.[38] Mean endometrial thickness on day 77 was 6.3 mm in the placebo group compared with 5.7, 6.3 and 5.4 mm in the ulipristal acetate 2.5, 5 and 10 mg/day groups.[38]
- Hormonal profiles were not affected by ulipristal acetate treatment in healthy women.[38] Estradiol levels remained within the physiological range for follicular development in all treatment groups and there was no down-regulation over the 3-month treatment period.[38] Similarly, follicle-stimulating hormone levels were normal, and, despite a transient increase in LH levels in a small (n = 4) number of women, progesterone levels remained low (<3 ng/mL) in most recipients of ulipristal acetate 5 or 10 mg/day.[38] Ultrasound scans showed no significant impairment of follicular growth in any of the treatment groups.[38]

• Unlike mifepristone, ulipristal acetate does not appear to alter endometrial matrix or vascular morphology. Following 12 weeks' treatment with ulipristal acetate 2.5, 5 or 10 mg/day, endometrial vessels, collagen network and messenger RNA (mRNA) levels of VEGF-A were identical to baseline during the luteal phase.[39] In contrast, mifepristone-induced amenorrhoea was associated with increased microvessel density and glucocorticoid receptor expression and decreased stromal VEGF expression.[46]

• However, treatment with SPRMs may result in changes in the histological architecture of the endometrium.[47,48] Biopsies obtained from women who had received 3 months' treatment with one of four different progesterone-receptor modulators (which included ulipristal acetate) revealed evidence of glandular dilatation with each agent that was histologically distinct from proliferative or secretory endometrium.[47,48] Rather, the histological changes were designated as progesterone-receptor modulator-associated endometrial changes (PAEC) that should not be confused with endometrial hyperplasia.[35,48]

2. Pharmacokinetic Profile

There are currently no fully published data regarding the pharmacokinetics of ulipristal acetate in women with uterine fibroids. Therefore, this section discusses briefly the limited pharmacokinetic data in healthy female volunteers available from the EMC summary of product characteristics focusing on, where possible, the approved dosage of ulipristal acetate 5 mg/day.[35]

• Ulipristal acetate is rapidly absorbed following oral administration. A mean maximum plasma concentration (C_{max}) of 23.5 ng/mL was achieved in a median time of ≈1 hour (t_{max}) following administration of a single dose of ulipristal acetate 5 mg. The corresponding mean area under the plasma-concentration time curve from time zero to infinity (AUC_{∞}) value was 61.3 ng • h/mL.[35]

• The major active metabolite of ulipristal acetate, mono-N-demethylated-ulipristal acetate, has a C_{max} of 9.0 ng/mL, which is reached approximately 1 hour after ingestion of a single 5 mg dose; the corresponding AUC_{∞} value is 26.0 ng • h/mL.[35]

• Coadministration of oral ulipristal acetate 30 mg with a high-fat meal resulted in a C_{max} that was approximately 45% lower, a delayed t_{max} (from a median of 0.75 to 3 hours) and an AUC_{∞} that was 25% higher than with the fasted state.[35] Similar results were observed for the active mono-N-demethylated metabolite. The effect of food is not thought to be clinically relevant.[35]

• Ulipristal acetate is highly bound (>98%) to plasma proteins that include albumin, α-1-acid glycoprotein, high-density liporotein cholesterol and low-density lipoprotein cholesterol.[35]

• After ingestion, ulipristal acetate is extensively metabolized in the liver by cytochrome P450 (CYP) 3A4 to its active mono-N-demethylated metabolite and subsequently to di-N-demethylated metabolites that are inactive.[35]

• The main route of elimination of ulipristal acetate is through the faeces, with <10% excreted in the urine.[35] The mean oral clearance rate for the 5 mg dose is approximately 100 L/hour, which results in a terminal half-life of approximately 38 hours.[35]

• Data from *in vitro* studies suggest that clinically relevant concentrations of ulipristal acetate and its active metabolite do not inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4, or induce CYP1A2.[35] However, coadministration with moderate or potent inhibitors of CYP3A4 (e.g. ketoconazole, ritonavir, nefazodone) may lead to increased plasma levels of ulipristal acetate.[35] In contrast, coadministration with inducers of CYP3A4 (e.g. rifampin, carbamazepine, phenytoin, St John's wort) may lead to decreased plasma levels of ulipristal acetate.[35] Consequently, coadministration of ulipristal acetate with these agents is not recommended.[35]

• Although ulipristal acetate is not a substrate for P-glycoprotein *in vitro*, clinically relevant concentrations may inhibit the enzyme in the gastrointestinal wall during absorption.[35] Consequently, plasma levels of drugs that are substrates of P-glycoprotein (e.g. dabigatran etexilate, digoxin) may be increased when coadministered with ulipristal acetate.[35] In the absence of any clinical data, coadministration of ulipristal acetate with substrates of P-glycoprotein is not recommended.[35]

• There are no pharmacokinetic data available for ulipristal acetate in women with impaired renal or hepatic function. However, as a result of its CYP-mediated clearance, hepatic impairment is expected to alter the elimination of ulipristal acetate, resulting in increased exposure (section 5).[35]

3. Therapeutic Efficacy

The clinical efficacy of oral ulipristal acetate 5 or 10 mg/day was evaluated in two, fully published, randomized, double-blind, parallel-group, multinational, placebo- (PEARL I)[36] or active-comparator-controlled, double-dummy (PEARL II)[37] phase III trials in women aged 18–50 years with symptomatic fibroids and excessive uterine bleeding.

Uterine bleeding was assessed using a self-reported pictorial blood-loss assessment chart (PBAC) in which scores range from 0 to >500, with higher numbers indicating more bleeding.[36,37] Eligible patients had a PBAC score >100 during days 1 to 8 of menstruation, a myomatous uterus equivalent in size to a uterus of ≤16 weeks' gestation, at least one fibroid ≥3 cm in diameter but no fibroid >10 cm in diameter (measured by ultrasound) and a body-mass index (BMI) score of 18–40 kg/m^2 at baseline.[36,37] In PEARL I, patients were additionally required to have fibroid-related anaemia (haemoglobin level ≤10.2 g/dL) and were receiving 80 mg of iron supplementation once daily in addition to the study drug.[36] Patients with a history of uterine surgery, endometrial ablation or uterine artery embolization, gynaecological cancer, endometrial hyperplasia, uterine polyps or ovarian cysts were excluded from the trials.[36,37]

Baseline characteristics were well matched between treatment arms in the two trials; there was a mean age of 40.1–42.0 years, a mean BMI score of 24.6–26.2 kg/m^2 and most (84–90%) patients were Caucasian.[36,37] Patients presented with a median PBAC score of 271–386, a median uterine volume of 197.8–337.6 cm^3 and mean haemoglobin levels of 9.3–12.4 g/dL.[36,37] Median total fibroid volume ranged from 61.9 to 100.7 cm^3 in PEARL I[36] and from 47.6 to 79.6 cm^3 in PEARL II,[37] which measured the three largest fibroids only.

The primary endpoint in both trials was the proportion of patients with controlled uterine bleeding at week 13, which was defined as PBAC score (summed over the preceding 28-day period) of <75.[36,37] The median change from baseline in total fibroid volume at week 13 was a coprimary endpoint in the PEARL I trial (measured by MRI with centralized readings).[36] In the PEARL II trial, the coprimary objectives were to show a superior tolerability profile for ulipristal acetate versus leuprolide acetate in terms of serum estradiol levels and the incidence of hot flush (discussed in section 4).[37] Furthermore, the noninferiority of ulipristal acetate with leuprolide acetate was established if the noninferiority margin for the percentage of patients with a PBAC score <75 was less than or equal to −20%.[37] Efficacy analyses were conducted in the modified intent-to-treat[36] or per-protocol population[37] with missing values imputed from the last observation carried forward.

Pain was assessed using the Short-Form McGill Pain Questionnaire, which uses scores ranging from 0 to 45; median baseline scores ranged from 6.5 to 9.0 across both trials.[36,37] At the end of the trials if no surgery was performed, endometrial biopsies were assessed for PAEC as described in section 1.[36,37]

In PEARL I, patients were randomized to receive ulipristal acetate 5 or 10 mg once daily or placebo, with randomization stratified according to haemocrit levels (≤28% or >28%) or race (Black or other).[36] In PEARL II, patients were randomized to ulipristal acetate 5 or 10 mg once daily or a once-monthly intramuscular injection of leuprolide acetate 3.75 mg, with randomization stratified according to race only.[37] In both trials, treatment was initiated during the first 4 days of menstruation and was continued for 13 weeks.[36,37] After which time, no further pharmacological therapy was administered, but pre-specified exploratory follow-up visits were performed at weeks 17, 26 and 38 and patients were eligible for surgery if required.[36,37]

Discussion in this section focuses on the approved dosage of ulipristal acetate 5 mg once daily; data from the 10 mg once-daily treatment arm are included, where appropriate, for completeness.

Table I. Efficacy of oral ulipristal acetate in adult women with uterine fibroids. Results from the pre-planned 13-week analyses of the randomized, double-blind, (double-dummy[37]), parallel-group, multinational, phase III PEARL trials in women aged 18–50 years with symptomatic fibroids and excessive uterine bleeding.[36,37] Efficacy analyses were evaluated using the modified intent-to-treat[36] or per-protocol[37] population, and missing values were imputed using the last observation during the preceding 28 days carried forward

Treatment regimen (mg/day)[c]	No. of evaluable pts	PBAC score <75[a]		Fibroid volume[b]	
		% pts[d]	Between-group difference (95% CI)	Median % change from BL	Between-group difference (95% CI)
PEARL I					
UPA 5	95	91	73 (55, 83)**	–21.2[e]	–22.6 (–36.1, –8.2)*
UPA 10	94	92	74 (56, 84)**	–12.3[e]	–18.2 (–33.0, –5.2)*
PL	48	19		+3.0[e]	
PEARL II					
UPA 5	93	90	1.2 (–9.3, 11.8)[f]	–36	NR
UPA 10	95	98	8.8 (0.4, 18.3)[f]	–42	NR
LPA[g]	93	89		–53	

a Summed over the preceding 28-day period.

b Total fibroid volume was measured in PEARL I by MRI with centralized readings. The three largest fibroids were measured in PEARL II by ultrasound.

c The approved dosage of ulipristal acetate is 5 mg/day.

d Primary endpoint.

e Coprimary endpoint.

f Noninferiority of UPA with LPA was established, as the prespecified lower limit of the CI was more than –20%.

g Pts received a depot formulation of LPA 3.75 mg by intramuscular injection once monthly.

BL = baseline; **LPA** = leuprolide acetate; **NR** = not reported; **PBAC** = pictorial blood-loss assessment chart; **PL** = placebo; **pts** = patients; **UPA** = ulipristal acetate; * $p < 0.01$, ** $p < 0.001$ vs PL.

- Oral ulipristal acetate treatment was effective in controlling excessive uterine bleeding in women with uterine fibroids. The recommended once-daily regimen of ulipristal acetate 5 mg controlled excessive bleeding in at least 90% of patients following 13 weeks' treatment (table I).[36,37]
- In the PEARL I trial, a significantly greater proportion of patients receiving ulipristal acetate 5 mg once daily compared with those receiving placebo achieved a PBAC score <75 following 13 weeks' treatment (primary endpoint).[36]
- In the PEARL II trial, a once-daily regimen of ulipristal acetate was no less effective than intramuscular leuprolide acetate administered once monthly in controlling excessive bleeding in women with uterine fibroids.[37] Following 13 weeks' treatment, ulipristal acetate 5 mg was noninferior to leuprolide acetate with regard to the percentage of patients with PBAC scores <75 (primary endpoint), as the lower limit of between-group difference for both dosage groups was greater than the prespecified margin of –20% (table I).[37]
- Excessive uterine bleeding was controlled rapidly with ulipristal acetate treatment. In the PEARL I trial, more than 75% of recipients of ulipristal acetate 5 mg/day achieved PBAC scores of <75 by day 8 compared with 6% of recipients of placebo; approximately half of recipients of ulipristal acetate 5 mg/day were amenorrhoeic by day 10.[36] Furthermore, excessive uterine bleeding was controlled significantly ($p < 0.001$) more rapidly for recipients of ulipristal acetate 5 mg/day than for recipients of leuprolide acetate in the PEARL II trial.[37] Approximately 85% of patients in the ulipristal acetate 5 mg/day group and 62% of patients in the leuprolide acetate group achieved controlled bleeding within the first 10 days of treatment (values read from a graph); the median times to amenorrhoea were 7 and 21 days, respectively.[37]
- Ulipristal acetate reduced fibroid volume in both trials.[36,37] The recommended once-daily regimen of ulipristal acetate 5 mg resulted in a median reduction in fibroid volume of at least 21% following 13 weeks' treatment (table I).[36,37]

- In PEARL I, a significantly greater median reduction from baseline in total fibroid volume was observed in the ulipristal acetate 5 mg once-daily treatment arm than in the placebo arm following 13 weeks' treatment in the PEARL I trial (coprimary endpoint).[37] Furthermore, for recipients of ulipristal acetate who did not undergo fibroid surgery, the reductions in total fibroid volume were maintained up to week 38 of the follow-up period.[37]
- In PEARL II, there was no significant difference between the ulipristal acetate and leuprolide acetate treatment arms in median volume reductions from baseline in the three largest fibroids (measured by ultrasound) at week 13 of the trial (table I).[37] However, by week 38 of the follow-up period in those women who did not undergo fibroid surgery, the median change from baseline in fibroid volume was −44.8% in the ulipristal acetate 5 mg/day group and −16.5% in the leuprolide acetate group (significance not evaluated).[37]
- Ulipristal acetate also reduced uterine volume in both trials following 13 weeks' treatment. In the PEARL I trial, significantly more recipients of ulipristal acetate 5 mg/day achieved at least a 25% reduction in uterine volume than recipients of placebo (34% vs 6%; $p < 0.001$).[36] Leuprolide acetate was associated with a significantly greater median reduction from baseline in uterine volume than ulipristal acetate 5 mg/day (47% vs 20%; level of significance not reported) in the PEARL II trial.[37] On the other hand, by week 38 of the follow-up period in women who did not undergo fibroid surgery, there was a 22% reduction in uterine volume for recipients of ulipristal acetate 5 mg/day compared with a reduction of 11% for recipients of leuprolide acetate (significance not evaluated).[37]
- Ulipristal acetate reduced pain, assessed by the Short-Form McGill Pain Questionnaire, at week 13 of both trials. In the PEARL I trial, the median change from baseline in pain score was significantly greater for recipients of ulipristal acetate 10 mg/day than placebo (−5.6 vs −2.5; $p = 0.04$) but not for recipients of ulipristal acetate 5 mg/day (−5.0).[36] In the PEARL II trial, the median change from baseline was −5.0 for recipients of ulipristal acetate 5 mg/day, −6.0 for recipients of ulipristal acetate 10 mg/day and −5.5 for recipients of leuprolide acetate and was not significantly different.[37]
- At the end of the 13-week treatment period, menstruation returned after a mean period of 30–34 days in the ulipristal acetate treatment groups and 43 days in the leuprolide acetate group.[36,37] During the follow-up period of both PEARL trials, approximately half of patients in each treatment arm underwent fibroid surgery.[36,37]

4. Tolerability

This section focuses on the tolerability of ulipristal acetate in women with uterine fibroids with data mostly derived from the two 13-week, randomized, double-blind, phase III PEARL trials discussed in section 3.[36,37] Additional tolerability data from a pooled analysis of all patients receiving both ulipristal acetate 5 and 10 mg/day dosages in these two trials ($n = 393$) are available from the EMC summary of product characteristics[35] and the European Medicine Agency's assessment report.[49] There are currently no longer-term tolerability data regarding the use of ulipristal acetate in this patient group.

- Oral ulipristal acetate was generally well tolerated in women with uterine fibroids in both PEARL trials.[36,37] Pooled data showed that the most frequent adverse events that occurred in both trials were amenorrhoea, endometrial thickening and headache (amenorrhoea is considered to be a desirable outcome in this patient group).[35] The majority of adverse events were mild to moderate in intensity (94.9%), did not lead to treatment-related discontinuation (99.3%) and resolved spontaneously.[35]
- The incidence of serious adverse events was low in both trials. During the treatment period and over a further follow-up period of 6 months duration, two patients in each of the ulipristal acetate treatment arms experienced at least one serious adverse event compared with six patients in the placebo arm in the PEARL I trial.[36] There were eight serious adverse events in the ulipristal acetate 5 mg/day group, five in the ulipristal acetate 10 mg/day group and six in the leuprolide

acetate 3.75 mg once-monthly group over the same period in PEARL II.[37]

- In the PEARL I trial,[36] the incidence of adverse events in recipients of ulipristal acetate 5 mg/day was similar to that in patients receiving placebo. There was no significant difference between the treatment arms in the frequency of any adverse event with an incidence ≥3% (figure 1).[36] The most common adverse events were headache and breast pain, tenderness or discomfort; the incidence of hot flush was <3% in all treatment arms.[36]
- Oral ulipristal acetate was associated with a significantly lower incidence of hot flush than intramuscular leuprolide acetate in the PEARL II trial (coprimary endpoint) [figure 2].[37] The frequency of all other adverse events that occurred with an incidence of ≥5% was not significantly different between the treatment arms.[37] The most common adverse events were hot flush and headache.[37]
- Plasma estradiol levels were maintained in the midfollicular range (60–150 pg/mL for a premenopausal woman) for all recipients of ulipristal acetate in both PEARL trials.[36,37] However, significantly lower estradiol levels were observed in the leuprolide acetate group compared with the ulipristal acetate 5 mg/day group (25 vs 64 pg/mL; $p < 0.001$) in the PEARL II trial (coprimary endpoint).[37] Otherwise, there were no clinically relevant effects of ulipristal acetate on corticotropin, thyrotropin, prolactin or glucose levels observed in either of the PEARL trials.[36,37]
- Ulipristal acetate treatment may result in endometrial thickening in some patients.[35] Pooled analysis showed that thickening of the endometrium (>16 mm measured by ultrasound or MRI) was observed in 10–15% of recipients of ulipristal acetate at the end of the treatment period of the PEARL trials. Thickening was reversed following the end of treatment and the return of menses.[35]
- Like other SPRMs, ulipristal acetate is associated with reversible changes to endometrial histology, denoted as PAEC (see section 1), that are distinct from endometrial hyperplasia.[35] At week 13 of the PEARL I trial, PAEC was observed in 62% of ulipristal acetate 5 mg/day recipients and 6% of those receiving placebo.[36] At week 13 of the PEARL II trial, PAEC was observed in 58% of ulipristal acetate 5 mg/day recipients and 12% of those receiving leuprolide

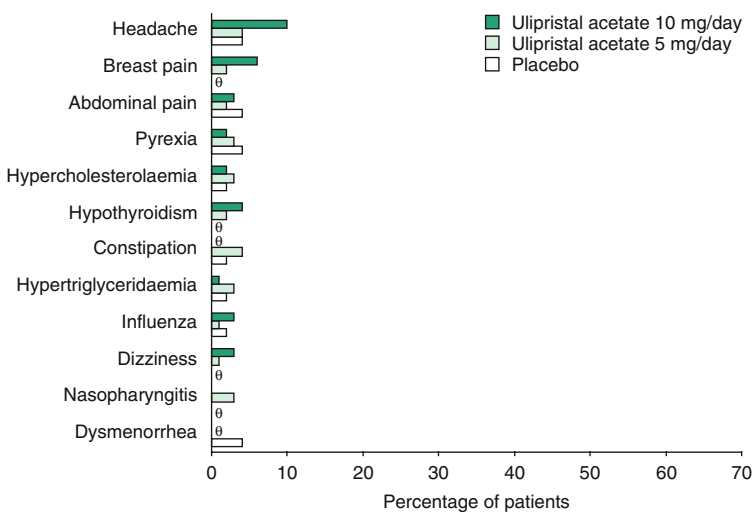

Fig. 1. Tolerability of oral ulipristal acetate in adult women aged 18–50 years with uterine fibroids. The most frequently reported (incidence of ≥3% in any treatment arm) adverse events from the randomized, double-blind, multinational, phase III PEARL I trial.[36] Adverse events that occurred after the first dose of the study drug and up to week 17 are included. Patients received 13 weeks' treatment with ulipristal acetate 5 (n = 95) or 10 mg/day (n = 98) or placebo (n = 48). θ = zero.

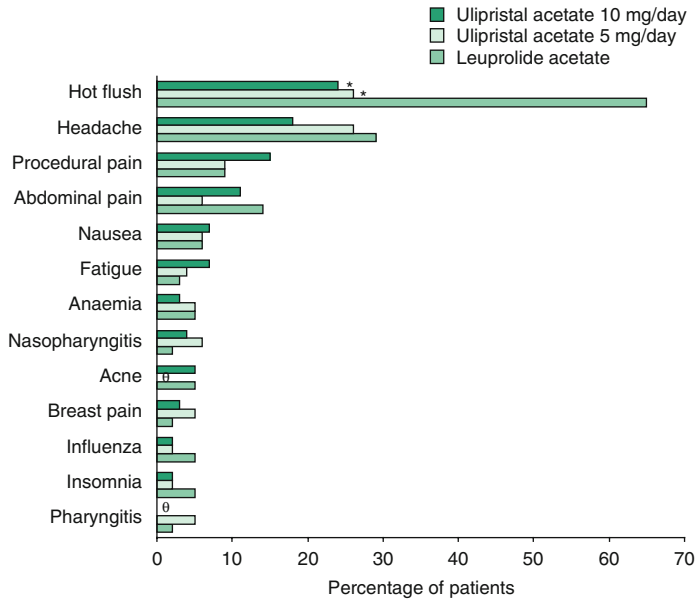

Fig. 2. Comparative tolerability of oral ulipristal acetate in adult women aged 18–50 years with uterine fibroids. The most frequently reported (incidence of ≥5% in any treatment arm) adverse events from the randomized, double-blind, double-dummy, multinational, phase III PEARL II trial.[37] Adverse events that occurred after the first dose of the study drug and up to week 17 are included. Patients received 13 weeks' treatment with ulipristal acetate 5 (n = 97) or 10 mg/day (n = 103) or intramuscular leuprolide acetate 3.75 mg once monthly (n = 101). θ = zero; * $p < 0.001$ vs leuprolide acetate.

acetate.[37] After a 6-month treatment-free follow-up period, the changes had mostly disappeared in both trials.[36,37]

5. Dosage and Administration

For adult women with uterine fibroids, the recommended dosage of oral ulipristal acetate is one 5 mg tablet once daily, which may be taken with or without food.[35] Treatment should start during the first week of the menstrual cycle and the total treatment period should not exceed 3 months. If a patient misses a dose, treatment should resume as quickly as possible. If the dose was missed by more than 12 hours, the patient should skip the missed dose and resume the normal dosage schedule.[35]

Ulipristal acetate should not be taken by women who are pregnant or breastfeeding.[35] It is also contraindicated in women with genital bleeding for reasons other than uterine fibroids and in those with uterine, cervical, ovarian or breast cancer. The concomitant use of progestogen-only pills, a progestogen-releasing intrauterine device or combined oral contraceptive pills with ulipristal acetate is not recommended and a non-hormonal method of contraception should be used instead.[35]

Unless closely monitored, ulipristal acetate is not recommended for use in patients with severe renal impairment or in those with moderate or severe hepatic impairment.[35] Its use in patients with severe asthma that is insufficiently controlled by oral glucocorticoids is also not recommended.[35]

Like other SPRMs, ulipristal acetate may affect the histology of the endometrium.[35] These changes are termed PAEC (discussed in section 1) and are distinct from endometrial hyperplasia. Approximately 10–15% of recipients of ulipristal acetate may experience endometrial thickening (>16 mm) during treatment.[35] The thickening usually disappears following the end of treatment and the return of menses.[35] If endometrial thickening persists within 3 months following the

end of treatment and the return of menses, as per usual clinical practice, appropriate investigation is recommended.[35]

Patients should be informed that ulipristal acetate treatment should lead to a marked reduction in menstrual blood loss within the first 10 days.[35] However, if excessive uterine bleeding persists, the patient should notify their physician. Menses normally return within 4 weeks of the end of the treatment course.[35]

Local prescribing information should be consulted for more details regarding contraindications, precautions and warnings.

6. Ulipristal Acetate: Current Status in Uterine Leiomyoma

Ulipristal acetate 5 mg/day is approved in the EU for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. The longer-term tolerability of ulipristal acetate has not been established and for this reason it is not approved for treatment periods of more than 3 months' duration.

Two well designed trials have shown that, following 13 weeks' treatment, oral ulipristal acetate 5 mg/day controlled excessive uterine bleeding in ≥90% of women with uterine fibroids. Ulipristal acetate 5 mg/day was more effective than placebo and was shown to be noninferior to intramuscular leuprolide acetate 3.75 mg once monthly in controlling uterine bleeding. Treatment with ulipristal acetate reduced uterine fibroid volume and, for patients who did not undergo surgery, the volume reduction was maintained for at least 6 months after discontinuing treatment. Over a 13-week treatment period, ulipristal acetate was generally well tolerated in women with uterine fibroids.

Disclosure

This manuscript was reviewed by ***T. Al-Shawaf***, Fertility Centre, St. Bartholomew's Hospital, London, UK; ***L. Bahmondes***, Human Reproduction Unit, Department of Obstetrics and Gynaecology, University of Campinas, Campinas, Brazil; ***P. Orihuela***, University of Santiago, Santiago, Chile.

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